REMARKS

In the claim listing above, claims 251-254, 261, 276-280, 282-283, 287 and 625 have been amended. No claims have been added or canceled. Accordingly, claims 251-287 and 625 continue to be presented for further examination in this application.

Claim Amendments

As just indicated, a number of claims (251-254, 261, 276-280, 282-283, 287 and 625) have been amended, largely for the sake of clarity and completeness.

Several claims (251-254, 276-277, 282, 287 and 625) have been amended to correct informalities (see Office Communication, pages 5-7).

Other claims (261, 277 and 283) have been amended to render the claimed subject matter more definite (see Office Communication, pages 7-8).

In three other claims (278-280), the term "labeled nucleotides" has been changed to "labeled transcription products" (claims 278 and 279) and to "labeled nucleic acid products" (claim 280).

No new matter is believed to have been inserted by any of the foregoing amendments to the claims.

Entry of the above amendments and claim listing is respectfully requested.

New Grounds of Rejection/Objections

Applicants acknowledge the indication in the Office Communication (page 2) regarding the new grounds of rejection and objection. They also appreciate the indication that the January 6, 2010 Office Communication is made non-final.

Priority

The Examiner's comments on pages 2-3 of the Office Communication regarding the priority date for this application are acknowledged. Applicants understand that the instant October 24, 2003 filing date has been used for prior art purposes.

Information Disclosure Statement

According to the Office Communication (page 3):

> Applicant's submission of an Information Disclosure Statement on June 19, 2009 is acknowledged. A signed copy is enclosed.
>
> The information disclosure statement filed on September 17, 2009 fails to comply with 37 CFR 1.97(c), because it does not contain either a statement as specified in 37 CFR 1.97(e) or the fee set forth in 37 CFR 1.17(p). Accordingly, it has been placed in the application file, but the information referred to therein has not been considered.

In response, Applicants are submitting herewith in Appendix C their Communication Directed To Their June 19, 2009 Information Disclosure Statement. It is believed that the content of this Communication (Appendix C) complies with the provisions of 37 C.F.R. §§1.97(c), 1.97(e) and/or the requirement for a fee set forth in 37 C.F.R. §1.17(p).

Objections to the Specification

The disclosure was objected to because of several informalities. According to the Office Communication (pages 3-4):

> . . . Figures 6 and 8-13 contain nucleic acid sequences that are greater than ten nucleotides in length, but have not been identified by the appropriate sequence identifier either in the drawing figure or in the "Brief Description of the Drawings" section (see MPEP 2422.02). Also, pages 16, 17, 31-35, and 37-42 contain nucleic acid sequences that are greater than ten nucleotides in length, but have not been identified by the appropriate sequence identifier.
>
> The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: The specification does not appear to provide proper antecedent basis for the following elements of: **claim 261** (Sequenase, phi29 DNA polymerase, mutational variations of either Sequenase or phi29 DNA polymerase, and combinations comprising either of these enzymes), **claim 268** (arabinosides), **claims 278-280** (polymerase-mediated incorporation of nucleotides labeled with a phosphorescent compound, a chemiluminescent compound, a chelating compound, an electron dense

compound, a magnetic compound, an intercalating compound, an energy transfer compound, an antibody, an antigen, a receptor, a hormone, an enzyme, and combinations comprising any of the aforementioned labels), and **claim 283** (glass slides or microtiter plates).

The use of the trademarks RNEASY, SUPERSCRIPT, and MINELUTE has been noted in this application (see at least page 31). These and any other trademarks in the specification should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. Appropriate correction is required.

The objections to the specification are respectfully traversed.

In response to the sequence identifiers in the drawing figure, the "Brief Description of the Drawings, and elsewhere in the specification, Applicants' attorney is attending to this matter and has referred it to their patent draftsmen for appropriate amendments and correction. As soon as the papers amending and correcting the sequence identifiers in the specification have been completed, they will be submitted in a supplemental paper to this Amendment.

Regarding the antecedent basis for subject matter in claims 261, 268, 278-280 and 283, Applicants are submitting herewith as Appendix A marked-up and clean versions of amended page 30 from the specification. Amended page 30 (Appendix A) contains the subject matter of claims 261, 268, 278-280 and 283. Under MPEP §608.01(l) Original Claims, an applicant may rely not only on the description and drawing as filed but also on the original claims if their content justifies it. Accordingly, the subject matter in amended page 30 (Appendix A) does not constitute the insertion of new matter.

Entry of amended page 30 (Appendix A) is respectfully requested.

Regarding the use of trademarks in the specification (for example, page 31), Applicants have corrected several trademarks as represented in marked-up and clean versions of amended page 31 accompanying their Amendment as Appendix B. Applicants' attorney is making a diligent review of the entire specification for the

purpose of making appropriate corrections to other trademarks. In the meantime, entry of amended page 21 (Appendix C) is respectfully requested.

Appropriate removal of the objections to the specification is respectfully requested.

Objections to the Claims

Several claims were objected to for various informalities. According to the Office Communication (pages 5-7):

> Claim 251 is objected to because of the following informalities: This claim appears to contain a typographical error at the end of part (iv) where "and" is recited. It would appear that this word is unnecessary. Also, replacing the word "by" in line 1 of step (c) with "using" is suggested to improve the language of the claim.
>
> Claim 252 is objected to because of the following informalities: This claim is grammatically incorrect. Replacing the word "are" in line with "is" and the word "are" in line 2 with "is" or "comprising" is suggested.
>
> Claim *253* is objected to because of the following informalities: This claim contains typographical errors in line 2, where "copes" and "form" are recited. It would appear that "copies" and "from", respectively, were intended.
>
> Claim 254 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter Of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 254 is drawn to the method of claim 252, wherein the homopolymeric sequences are present in the library of nucleic acid targets before or after isolation of the library from the biological source. Since the homopolymeric sequences must inherently be present in the library before or after the isolation step, claim 254 fails to further limit the method of claim 252.
>
> Claim 276 is objected to because of the following informalities: This claim appears to be missing words, such as "the synthesis of', after the word "wherein" in line 1.
>
> Claim 277 is objected to because of the following informalities: This claim contains a typographical error in line 2, where "nucleotides" is recited. It would appear that "nucleotide" was intended.
>
> Claim 282 is objected to because of the following informalities: Replacing the words "primer or nucleic acid construct is" with "primers or nucleic acid constructs are" is suggested to maintain consistency with claim 251.

Claim 287 is objected to because of the following informalities: Replacing the word "segment" in line 3 with "sequence" is suggested to maintain consistency with claim 251.

Claim 287 is also objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to fUrther limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 287 is drawn to the method of claim 251, wherein at least one of the bases of the nucleotide analogues is different from the bases comprising the homopolymeric segment. Since the nucleotide analogues are part of primers that are complementary to the homopolymeric segment, the analogue bases would necessarily have to be different from the bases comprising the homopolymeric segment, as complementary base pairing would not occur otherwise. Accordingly, claim 287 does not appear to further limit the method of claim 251. Claim 625 is objected to because of the following informalities: This claim contains minor typographical errors. The following changes are suggested: (a) replacing the words "comprise", "their", and "ends" in line 3 of step (ii) with "comprises", "the", and "end", respectively, (b) inserting a hyphen between the words "template" and "dependent" in line 1 of step (iii), and (c) deleting the word "and" at the end of step (iii).

The objections to the claims are respectfully traversed.

In response, Applicants respectfully point out that all of the claims, including claim 287, have been appropriately corrected to cure the informalities cited in the Office Communication.

With respect to the improper dependency of claim 287, Applicants respectfully point out that the primers comprise the complement to the homopolymeric sequences. When used in the case where it comprises a homopolymeric sequence, the primer is not barred from providing non-homologous sequences. There are described in the specification the 3' end as comprising non-homologous sequences for the purposes of making a so-called anchoring sequence which will bind to the junction of a homopolymeric sequence and a non-homologous sequence in a target analyte.

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the claim objections.

Enz-60(CIP)

The Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 261, 277, 280, 283, 284, and 286 stand rejected for indefiniteness under 35 U.S.C. §112, second paragraph. According to the Office Communication (pages 7-8):

> Claim 261 contains the trademark/trade names SEQUENASE, SENSISCRIPT, and OMNISCRIPT. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Exparte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe particular polymerases and, accordingly, the identification/description is indefinite.
>
> Claim 277 is vague and indefinite, because it is not clear from the claim language as to what nucleic acid must be copied in the presence of labeled nucleotides. Claim 277 is drawn to the method of claim 273, further comprising synthesizing a nucleic acid copy in the presence of at least one labeled nucleotide, thereby generating a labeled nucleic acid copy product. Claim 273 recites a step of conducting a transcription reaction, which generates a copy of a template nucleic acid. Claim 273 ultimately depends from claim 251, which also recites a nucleic acid copying step in step (c). As a result, the copying step recited in claim 277 could refer to the copying step in step (c) of claim 251, the transcription step of claim 273, or an additional copying step using the transcription product as a template. Since it is not clear from the claim language as to which of these nucleic acids must be copied, claim 277 is vague and indefinite.
>
> Claim 280 is also indefinite, because it depends from claim 277.
>
> Claim 283 is indefinite, because it depends from a canceled claim — clam 289. For examination purposes, claim 283 has been treated as depending from claim 282.
>
> Claim 284 is indefinite, because it is unclear how a homopolymeric segment can be comprised of more than one type of nucleotide. Claim 284 is drawn to the method of claim 251, wherein the sequence of the homopolymeric segment is comprised of T, U, or any combination thereof. Since a homopolymeric sequence contains, by definition, only one type of nucleotide, it is unclear how a sequence comprised of T and U can be considered to constitute a homopolymeric sequence.

> Claim 286 is vague and indefinite, because it is entirely unclear as to what the limitations recited therein are intended to encompass. Claim 286 is drawn to the method of claim 251, wherein at least one of the nucleotide analogues comprises a portion of the homopolymeric sequence. Since the primers that contain said nucleotide analogues are complementary to the homopolymeric sequence, it is unclear how a nucleotide analogue contained therein can "comprise a portion of the homopolymeric sequence" as required by claim 286.

The indefiniteness rejection is respectfully traversed.

At the outset, Applicants respectfully note that the three trademarks recited in claim 261 (SEQUENASE®, SENSISCRIPT® AND OMNISCRIPT®) have been replaced by appropriate generic descriptions.

Further, claim 277 has been amended to recite "further comprising the step of synthesizing a nucleic acid copy in the presence of at least one labeled nucleotide *while carrying out said transcription reaction*, thereby generating labeled nucleic acid copy products." Thus, claim 277 now conforms with claim 273 from which it depends.

The matter of claim 280 has been handled by the just described amendment to claim 277.

The improper claim dependency in claim 283 has been corrected by making it depend from claim 282 – and not canceled claim 289.

Regarding the indefiniteness of claim 284, it is believed that this claim passes muster for clarity under the statute. A homopolymeric sequence is not necessarily confined to a single type of nucleotide, such as T or U. It is possible to conceive and synthesize a homopolymeric sequence composed of more than one type of nucleotide, provided that the sequence does not vary in its composition. Thus, a sequence composed of TUTUTUTU . . . could still be considered *homopolymeric*.

Finally, regarding claim 286, the language has been changed to recite "wherein said nucleotide analogues comprise a portion of said homopolymeric sequence." It is believed that the foregoing amendment renders claim 286 sufficiently definite under the statute.

Enz-60(CIP)

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the indefiniteness rejection.

The First Rejection Under 35 U.S.C. §112, First Paragraph

Claims 278-280 stand rejected on enablement grounds under 35 U.S.C. §112, first paragraph. According to the Office Communication (pages 9-11):

> . . . because the specification, while being enabling for using a polymerase to incorporate nucleotides having a fluorescent, phosphorescent, chemiluminescent, hapten, or intercalating label, does not reasonably provide enablement for using a polymerase to incorporate nucleotides having a label that is a chelating compound, an electron dense compound, a magnetic compound, an energy transfer compound other than fluorescent dyes, an antibody, an antigen, a receptor, a hormone, a ligand, an enzyme, or any combination thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.
>
> Factors to be considered in determining whether a disclosure meets the enablement requirement of35 USC 112, first paragraph, have been described by the court in *In re Wands,* 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,
>
> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, *(5)* the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.
>
> Claims 278-280 are drawn to the methods of claims 275-277, respectively, wherein the labeled nucleotides incorporated via polymerase activity are labeled with a fluorescent compound, a chemiluminescent compound, a phosphorescent compound, a chelating compound, an electron dense compound, a magnetic compound, an intercalating compound, an energy transfer compound, an antibody, an antigen, a hapten, a receptor, a hormone, a ligand, an enayme, or any combination of the preceding. The claimed methods are classified in the unpredictable arts of chemistry and molecular biology and are associated with a high level of skill in the art.
>
> The scope of claims 278-280 is very broad, because they encompass polymerasemediated incorporation of a nucleotide conjugated to virtually any imaginable label. The labels encompassed by the claims

have vastly different chemical structures and physical properties and would require the use of very different chemistries to be conjugated to nucleotides. The labels encompassed by the claims would also each present unique challenges with respect to polymerase-mediated incorporation.

As noted above in section 4, the specification only provides proper antecedent basis for polymerase-mediated incorporation of nucleotides attached to fluorescent labels or haptens, and accordingly, the disclosure of the instant application provides absolutely no guidance as to the methods for obtaining nucleotides conjugated to the above compounds or using them in a polymerase-mediated nucleic acid labeling reaction.

It was generally known in the art at the time of the invention that nucleotides conjugated to chemiluminescent compounds, fluorescent compounds, phosphorescent compounds, intercalating compounds, energy transfer compounds in the form of fluorescent dyes, and haptens could be used to label nucleic acids via polymerase-mediated nucleotide incorporation. (see, for example, paragraphs *45-5* 1 of Lapidus et al. (US 2005/0100932 Al; newly cited)). The art also teaches that many polymerases are either unable to incorporate labeled nucleotides or are only capable of low-efficiency incorporation, particularly when the label in question is large and "bulky" (see, for example, pages 2630 and 2634 of Giller et al. (Nucleic Acids Research (2003) 31(10): 2630-2635; newly cited)).

The quantity of experimentation necessary to practice the full scope of the claimed methods is very large. In order to practice the full scope of the claimed methods, the ordinary artisan would be required to undertake the following types of non-routine and unpredictable experimentation: (i) conjugating of nucleotides to each different type of label that was unconventional in the art, such as receptors and antibodies, which may include the development of novel methods of conjugation and (ii) demonstrating that polymerases are capable of incorporating each of the different resulting labeled nucleotides in a template-dependent process. Each different type of label encompassed by the claims presents different issues in terms of conjugation chemistry and likelihood of serving as a polymerase substrate. Given the lack of guidance in the art and the specification regarding the majority of the labels recited in the claims and the negative teachings in the art concerning polymerase-mediated incorporation of labeled nucleotides, this large amount of experimentation would necessarily be associated with a high degree of unpredictability. Accordingly, since a very large amount of highly unpredictable experimentation would be required in order to practice the full scope of the claimed methods, claims 278-280 fail to satis& the enablement requirement of 35 U.S.C. 112, first paragraph.

The enablement rejection is respectfully traversed.

With reference to page 9 in the Office Communication regarding the enablement for using a polymerase to incorporate nucleotide, Applicants offer the following remarks. Claims 278, 279 and 280 have been amended to by deleting the term "labeled nucleotides" and substituting "labeled transcription products" in claim 278, "labeled transcription products" in claim 279 and "labeled nucleic acid products" in claim 280. In addition to incorporation of labeled nucleotides that comprise labels such as a hapten or a fluorescent molecule, a well-known method for labeling comprises incorporation of modified nucleotides that contain a reactive group such an allylamine group. These groups can be used for post-synthetic processes such as adding as chelating compound, an electron dense compound, a magnetic compound and the other labels that are listed in the Office Communication (page 9) as being non-enabled for direct incorporation.

With regard to the comments in the Office Communication (page 10) regarding the breadth of scope in regards to use of practically any label, this is commensurate with the invention in that the particular means that are used for labeling is irrelevant to the novelty of the invention itself, and the invention should be able to avail itself of any means that have been described in the literature.

In view of the above claim amendments and foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the enablement rejection.

The Second Rejection Under 35 U.S.C. §112, First Paragraph

Claims 278-280 stand rejected for written description grounds under 35 U.S.C. §112, first paragraph. According to the Office Communication (pages 12-14):

> The central inquiry when considering written description is whether an ordinary artisan would reasonably conclude that Applicant was in possession of the claimed invention at the time of filing (see MPEP 2163 and *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1566-67,43 USPQ2d 1398, 1404-05 (Fed. Cir. 1997); *Hyatt v. Boone*, 146 F.3d 1348, 1354, 47 USPQ2d 1128, 1132 (Fed. Cir. 1998)).
>
> According to Revision I of the Written Description Training Materials (posted 4/11/08 at http://www.uspto.gov/web/menu/written/pdf),

the following factors should be considered, when evaluating a claim for compliance with the written description requirement: (a) actual reduction to practice, (b) disclosure of drawings or structural chemical formulas (c) sufficient relevant identifying characteristics (d) method of making the claimed invention, (e) level of skill and knowledge in the art, and (f) predictability in the art (see page 1 of the Training Materials).

Claims 278-280 are drawn to the methods of claims 275-277, respectively, wherein the nucleotides incorporated via polymerase activity are labeled with a fluorescent compound, a chemiluminescent compound, a phosphorescent compound, a chelating compound, an electron dense compound, a magnetic compound, an intercalating compound, an energy transfer compound, an antibody, an antigen, a hapten, a receptor, a hormone, a ligand, an enayme, or any combination of the preceding. The claimed methods are classified in the unpredictable arts of chemistry and molecular biology and are associated with a high level of skill in the art. As discussed above, the scope of claims 278-280 is very broad, because they encompass polymerase-mediated incorporation of a nucleotide conjugated to virtually any imaginable label. The labels encompassed by the claims have vastly different chemical structures and physical properties and would require the use of very different chemistries to be conjugated to nucleotides. The labels encompassed by the claims would also each present unique challenges with respect to polymerase-mediated incorporation.

As noted above in section 4, the specification only provides proper antecedent basis for polymerase-mediated incorporation of nueleotides attached to fluorescent labels or haptens, and accordingly, the disclosure of the instant application provides absolutely no guidance as to the methods for obtaining nucleotides conjugated to the above compounds or using them in a polymerase-mediated nucleic acid labeling reaction. As a result, the specification does not contain an actual reduction to practice of methods of using a polymerase to incorporate nucleotides labeled with a chelating compound, an electron dense compound, a magnetic compound, an energy transfer compound other than a fluorescent dye, an antibody, an antigen, a receptor, a hormone, a ligand, an enayme, or any combination of the preceding. The specification also fails to teach the relevant identifying characteristics required to satisfy the written description requirement, since there is no discussion regarding methods for making or using such labeled nucleotides.

Since, as evidenced by the teachings of Giller (see above), many polymerases are either unable to incorporate labeled nucleotides or are only capable of low-efficiency incorporation, particularly when the label in question is large and "bulky", the polymerase-mediated incorporation of nucleotides labeled with the aforementioned labels is necessarily associated with a high degree of unpredictability and requires a high level

> of skill in the unpredictable arts of chemistry and molecular biology. Accordingly, it must be concluded that Applicant was not in possession of the full scope of the methods recited in claims 278-280 at the time of filing.

The written description rejection is respectfully traversed.

At the outset, Applicants respectfully note that page 31 of the specification has been amended to recite the subject matter of claims 261, 268, 278-280 and 283. Since the original claims are part of Applicants' original disclosure, that in and of itself should obviate the present rejection.

Beyond that, however, Applicants wish to point out that in the previous enablement rejection, they described a well-known labeling method that comprises incorporating modified nucleotides which contain a reactive group such an allylamine group – and to such a reactive group, numerous labeling groups, even *bulky* groups, can be attached in post-synthetic processes.

In view of the above claim amendments and foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the written description rejection.

Commonality of Ownership

Applicants assert that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made.

The First Rejection Under 35 USC §103

Claims 251, 252, 254, 256, 259-264, 269-273, 275, 281, 285-287, and 625 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Laird et al. (EP 1 201 768 A2; cited previously). According to the Office Communication (pages 15-20):

> These claims are drawn to method for copying a library of target nucleic acids using primers that are complementary to a homopolymeric sequence in the library of target nucleic acids and contain at least one nucleotide analogue at the 3'-terminus having a modification at the 2' position of the ribose ring.

Lin teaches methods for generating eDNA libraries from cells (see Figure 1 and column 2, line 42 — column 3, line 16).

Regarding claims 251, 264, and 281, Lin teaches a method for synthesizing one or more copies of a library of target nucleic acids comprising:

(a) providing:

(i) a library of target RNA molecules (see column 6, lines 10-17 and column 2, lines 45-5 1; see also Figure 1, step a),

(ii) primers comprising sequences complementary to homopolymeric sequences in the library of nucleic acid targets (see Figure 1, column 2, lines 52-56, column 6, lines 17-2 1 and lines 60-65),

(iii) synthesizing reagents for the synthesis of a nucleic acid copy (see column 2, lines 52-55 and column 6, lines 15-24), and

(iv) addition reagents for addition of a non-inherent universal detection target (UDT) comprising terminal deoxynucisotidyl transferase (TdT) (column 2, lines 5 8-65 and column 6, lines 25-32),

(b) annealing the primers to the homopolymeric sequences in the library of target nucleic acids (see Figure 1, column 2, lines 52-56, and column 6, lines 17-2 1)

(c) extending the annealed primers using the synthesizing reagents to generate at least one copy of the target nucleic acids (Figure 1, column 2, lines 52-56, and column 6, lines 17-21), and

(d) adding a non-inherent UDT to the extended primers (see Figure 1, column 2, lines 58-65, and column 6, lines 25-32, where the polyG tail is added to the extended primers).

Regarding claim 252, Lin teaches that the library of targets is isolated from a biological source (column 6, lines 15-17).

Regarding claims 254 and 256, Lin teaches that the homopolymeric sequences, which are poly A sequences, are present prior to the isolation of the library of targets from the biological source (see Figure 1, step a and column 6, lines 15-25).

Regarding claim 261, Lin teaches that the synthesizing reagents comprise Taq DNA polymerase (see column 7, line 5, for example).

Regarding claims 262 and 263, Lin teaches that the method of claim 251 further comprises:

(a) providing additional synthesizing reagents for synthesizing a complementary copy of the copy obtained in step (c) (see Figure 1, step c and column 6, lines 43-49)

(b) separating the nucleic acid target from the first nucleic acid copy (see Figure 1, step c and' column 6, lines 43-49, where synthesis of the complementary copy by Pwo polymerase inherently results in separation of the target from the first copy)

(c) synthesizing the complementary copy using reverse primers complementary to sequences in the UDT (Figure 1, step c and column 6,

lines 43-49, where the poly(dC) primer is taught).

Regarding claims 269-272, the forward and reverse primers taught by Lin comprise a production center, since they contain T7, T3, or SP6 promoter sequences which fttnction to produce multiple copies of the target nucleic acid sequence (see Figure 1 and column 6, lines 15-65; see also column 3, lines 28-31).

Regarding claim 273, Lin teaches that the method of claim 271 further comprises:

(a) providing reagents for RNA transcription comprising RNA polymerase (see Figure 1, step d, column 2, line 66 — column 3, line 4, and column 6, lines 35-55),

(b) providing dNTPs and NTPs (column 6, lines 3 5-55), and

(c) creating a transcript (column 6, lines 3 5-55 and Figure 1, step d).

Regarding claim 275, LIn teaches condcucting the transcription reaction in the presence of labeled nucleotides to generate labeled transcription products (column 5, lines 19-23).

Regarding claim 285, Lin teaches that the homopolymeric segment is comprised of poly A (see Figure 1, column 3, lines 32-39, and column 6, lines 15-65).

Regarding claim 625, Lin teaches a method for synthesizing a copy of at least one nucleic acid target comprising:

(a) providing:

(I) at least one nucleic acid target (see column 6, lines 10-17 and column 2, lines 45-5 1; see also Figure 1, step a),

(ii) at least one primer or nucleic acid construct complementary to a poly A sequence in the nucleic acid target, wherein the primer or nucleic acid construct comprises one or more terminal nucleotides at the 3' end (see Figure 1, column 2, lines 52-56, and column 6, lines 17-21), and

(iii) template-dependent synthesis reagents for the synthesis of a nucleic acid copy (column 2, lines 52-55 and column 6, lines 15-24),

(b) annealing the primer or nucleic acid construct to the target nucleic acid (see Figure 1, step b, column 2, lines 52-56, and column 6, lines 17-21), and

(c) synthesizing a copy of the target nucleic acid using the target nucleic acid as a template and extending the primer or nucleic acid construct using the synthesizing reagents (Figure 1, step b, column 2, lines 52-56, and column 6, lines 17-2 1).

Lin does not teach that the primers contain 3' terminal nueleotides that are substituted with nucleotide analogues containing a modification at the 2' position of the ribose ring as required by claims 251, 259, 286, and 287. Lin also does not teach the use of bhimerie primers as required by claim 260.

Laird teaches methods for conducting PCR amplification using

modified primers (see abstract and paragraphs 12-18). Laird teaches that the disclosed modified primers increase the time required for initial primer extension, and thereby, reduce nonspecific amplification of the target nucleic acid (paragraph 37).

Regarding claims 251, 259, and 625, Laird teaches conducting PCR using primers in which 1-3 of the 3' terminal nucleotides are modified nucleotides selected from 2'-O-methyl-nucleotides, 2'-fluoro-nucleotides, and 2'-amino-nucleotides (paragraphs 12-18).

Regarding claim 260, Laird teaches that the primers may contain additional nucleotide analogues (paragraph 20).

Regarding claim 286, the nucleotide analogues taught by Laird inherently comprise a portion (e.g. a sugar-phosphate backbone) of the homopolymeric sequence present in the library of nucleic acid targets.

Regarding claim 287, when incorporated into the oligo(dT) primers of Lin, the nucleotide analogues taught by Laird will necessarily have a base (thymine) that is different from the bases (adenine) comprising the homopolymeric sequence present in the library of nucleic acid targets.

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Laird to the method taught by Lin. An ordinary artisan would have been motivated to modify the primers taught by Lin to include the modified nucleotides (2'-0-methyl-nucleotides, 2'-fluoro-nucleotides, and 2'-amino-nucleotides) taught by Laird at the 3' terminus, since Laird taught that the presence of these modified nucleotides at the 3' terminus of an amplification primer reduced nonspecific amplification stemming from primer-dimer formation or misextension of the primer (paragraph 37). Combining the teachings of Lin and Laird would result in placement of at least one of the nucleotide analogs in the homopolymeric sequence comprising the 3' oligo(dT) tail of the primer taught by Lin. An ordinary artisan would have had a reasonable expectation of success in applying the teachings of Laird to the method taught by Lin, since Laird taught that the synthesis of primers containing the modified nucleotides was conducted using commercially available reagents and standard chemical synthesis methods known in the art (paragraphs 41-45). Thus, the methods of claims 251, 252, 254, 256, 259-264, 269-273, 275, 281, 285-287, and 625 are prima facie obvious over Lin in view of Laird.

The first obviousness rejection is respectfully traversed.

With regard to above obviousness rejection of claims 251+ in view of Lin et al. as the primary reference in view of Laird et al. as the secondary reference, Applicants would like to preface their remarks by noting later statements in the Office Communication:

> "Since Laird expressly defines non-specific amplification as any amplification other than that resulting from the hybridization of primer to its complementary target sequence in a target nucleic acid....."
> (as stated on pages 34, 36 and 38 in the Office Communication)

Applicants respectfully submit that the above statements represent an arbitrary broadening of the actual definition given by Laird et al. in their disclosure. Indeed, Laird et al. specifically state:

> "The term "non-specific amplification" refers to the amplification of nucleic acid sequences other than the target sequence which results from primers hybridizing to sequences other than the target sequence and then serving as substrates for primer extension." [0028] of Laird et al and emphasis added.

The Office Communication apparently adopts a definition that involves an interpretation of "non-specific amplification" being anything other than specific amplification whereas In contrast, Laird specifically limits non-specific amplification to be a product of inappropriate binding of a primer to a template and extension of the inappropriately bound primer on this template. Consequently, all of Laird's teachings are directed towards the ability of modified nucleotides to prevent or limit inappropriate binding/extension of primers with non-target templates.

The particular example of inappropriate targets being used for primer binding (and extension) is in the context of primer dimer formation, which is characterized by Laird in [0029] as follows:

> "Primer dimer is believed to result from primer extensions wherein another primer serves as a template .....".

Consequently, in addressing the various other references that are used in the combination of Laird with Lin, Applicants will continue to use the definition provided by Laird et al. and will not agree to or adopt the definition provided in the Office Communication, namely that Laird teaches the use of modified nucleotides for prevention of any and all forms of non-target amplification. As described above, this is not the case.

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As such, with regard to page 15 of the Office Action, Applicants believe that the combination of Lin and Laird do not render the invention of claim 251 obvious in that the problem that is solved by Laird is not presented or raised by Lin et al. The Office Communication purports to find motivation for the application of Laird to Lin on page 19 as:

> " . . . since Laird taught that the presence of modified nucleotides at the 3' terminus of an amplification primer reduced non-specific amplification stemming from primer-dimer formation or mis-extension of the primer."

Applicants wish to again point out that neither of these problems exist in Lin et a;. There is no description of a primer-dimer problem in Lin or any particular mechanism whereby such an amplicon would ever be formed. With regard to mis-extension by using inappropriate sequences, Lin describes a global amplification of any and all forms of mRNA. There is no description in Lin of a problem with using other sequences than the poly A tails or what particular problems such events would engender.

On the other hand, in the present invention of claim 251, the use of modified primers solves two potential problems 1) terminal transferase addition of nucleotides to primers that have not been extended by use of target mRNA templates; and 2) the use of unextended primers for promoter independent transcription by T7 RNA polymerase. Both of these types of nucleic acid synthesis results in target independent nucleic acid synthesis that would generate labeled material irrelevant to any analytes in the reaction. Consequently, Applicants have discovered that the use of modified nucleotides at the 3' terminus of primers can reduce these aberrant forms of nucleic acid synthesis. The problem that has been described to be solved by Laird et al. involves inappropriate bindings of primers to non-complementary sequences followed by their use as templates for extension reactions, neither of which is describes problem 1 or 2) above. As such, no particular motivation to apply the teachings of Laird to the method of Lin exists.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the first obviousness rejection.

The Second Rejection Under 35 USC §103

Claims 253, 255, 257, and 258 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Lin et al. (US 6,197,554 BI; cited previously) in view of Laird et al. (EP 1201788; cited previously) and further in view of Kustu et al. (US 6,242,189 BI; newly cited). The text of the second rejection is set forth on pages 20-21 in the Office Communication.

The Third Rejection Under 35 USC §103

Claims 265-268 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Lin et al. (US 6,197,554 BI; cited previously) in view of Laird et al. (EP 1201788; cited previously) and fttrther in view of Willis et al. (US 6,858,412; cited previously) and further in view of Moran et al. (Nucleic Acids Research (1996) 24(11): 2044-2052; cited previously). The text of the third rejection is set forth on pages 21-24 in the Office Communication.

The Fourth Rejection Under 35 USC §103

Claims 274 and 276 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Laird et al. (EP 1201788; cited previously) and further in view of Sousa et al. (US 5,849,546; cited previously). The text of the fourth rejection is set forth on pages 24-25 in the Office Communication.

The Fifth Rejection Under 35 USC §103

Claims 277, 278, and 280 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Lin et al. (US *6,197,554* Bi; cited previously) in view of Laird et al. (EP 1201788; cited previously) and further in view of Steffens et al. (Genome Research

(1995) 5: 393-399; cited previously). The text of the fifth rejection is set forth on pages 26-27 in the Office Communication.

The Sixth Rejection Under 35 USC §103

Claim 279 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Laird et al. (EP 1201788; cited previously) and further in view of Sousa et al. (US 5,849,546; cited previously) and further in view of Steffens et al. (Genome Research (1995) 5: 393-399; cited previously). The text of the sixth rejection is set forth on pages 28-29 in the Office Communication.

The Seventh Rejection Under 35 USC §103

Claims 282 and 283 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Lin et al. (US *6,197,554* B1; cited previously) in view of Laird et al. (EP 1201788; cited previously) and further in view of Stinear et al. (Applied and Environmental Microbiology (1996) 62(9). The text of the seventh rejection is set forth on pages 29-30 in the Office Communication.

The Eighth Rejection Under 35 USC §103

Claim 284 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Laird et al. (EP 1201788; cited previously) and further in view of Petrick et al. (Journal of Virological Methods (1997) 64: 147-159; newly cited). The text of the eighth rejection is set forth on pages 30-31 in the Office Communication.

The Ninth Rejection Under 35 USC §103

Claim 625 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Borson et al. (PCR Methods and Applications (1992) 2: 144-148; cited previously) in view of Laird et al. (EP 1201788; cited previously). The text of the ninth rejection is set

forth on pages 32-33 in the Office Communication.

With respect to the remaining obviousness rejections (Nos. 2-9), Applicants respectfully traverse each and every rejection as being founded on an improper foundation of Lin et al. In view of Laird et al. It stands to reason that because the primary and second references are insufficient to reach the bulk of Applicants' invention and claimed subject, the addition of other references will not logically solve the deficiencies of Lin's and Laird's disclosures. With respect to the ninth rejection which is based upon Borson et al. in view of Laird et al., again, the deficiencies of Laird are well described above and do not supplement the former's disclosure to reach the subject matter of claim 625.

In view of the foregoing remarks, Applicants respectfully request reconsideration of the remaining obviousness rejections.

Information Disclosure Statement

Applicants are filing concurrently with this paper their Information Disclosure Statement in order to bring several documents to the attention of the Examiner so that these documents can be made of record in this application and properly considered. Applicants' IDS contains a single sheet of Form PTO/SB/08a (01-08) and a single sheet of Form PTO/SB/08b (01-08) as well as three non-U.S. patent publications.

Applicants respectfully request that the documents submitted with their separately filed IDS be made of record and considered by the Examiner.

Early and favorable action is respectfully requested.

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SUMMARY AND CONCLUSIONS

A complete listing of the claims in this application are provided above. In the claim listing above, claims 251-254, 261, 276-280, 282-283, 287 and 625 have been amended.

This paper is accompanied by Applicants' Request For Extension Of Time (3 Months), their Information Disclosure Statement(s), and authorization for the fees therefor. No other fee or fees are believed due in connection with this paper. In the event that any other fee or fees are due, however, authorization is hereby given to charge the amount of any such fee(s) to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Early and favorable action is respectfully requested.

Respectfully submitted,

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APPENDIX A

In another embodiment of the present invention it is disclosed that labeled material intended for use in an array does not have to be used as a probe but can instead be used as a source of template material for carrying out further amplification procedures. Thus for instance, if the methods of the present invention have been used to generate a labeled library by a promoter in the second strand synthesis to produce sense RNA, the same primer that was used for the original first strand synthesis could be used with the labeled material to synthesize 1st strand cDNA and carry out a further cycle of amplification. On the other hand if a promoter was used in the 1st strand, thereby generating labeled antisense RNA, the same primer that was used for the second strand synthesis could be used to initiate cDNA synthesis from the labeled template. When a transcription is carried out in this new cycle, inclusion of labeled nucleotides could generate a sufficient amount of labeled probe to carry out the intended experiment with a microarray without having to go back to the original source.

Among synthesizing reagents are those comprising E. coli DNA Pol I, Klenow fragment of E. coli DNA Pol I, Bst DNA polymerase, Bca DNA polymerase, Taq DNA polymerase, Tth DNA polymerase, T4 DNA polymerase, T7 DNA polymerase, SEQUENASE® (T7 DNA polymerase with virtually no 3'→5' exonuclease activity), Φ 29 DNA polymerase, ALV reverse transcriptase, MuLV reverse transcriptase, RSV reverse transcriptase, HIV-1 reverse transcriptase, HIV-2 reverse transcriptase, SENSISCRIPT® (reverse transcriptase with amounts of RNA < 50 ng), OMNISCRIPT® (reverse transcriptase with amounts of RNA > 50 ng), any mutational variations of any of the preceding, or any combination of the preceding.

Terminator nucleotides comprise dideoxyribonucleotides, acyclic nucleotides, arabinosides or 3' amino nucleotides.

Labeled nucleotides comprise a fluorescent compound, a phosphorescent compound, a chemiluminescent compound, a chelating compound, an electron dense compound, a magnetic compound, an intercalating compound, an energy transfer compound, an antibody, an antigen, a hapten, a receptor, a hormone, a ligand, an enzyme, or any combination of the preceding.

Solid matrix comprises magnetic beads, latex beads, microtitre plates or glass slides.